The new post-genomic field of science

- Proteins are the primary target for most therapeutics
- New biomarkers for disease, toxicity and treatment
- Determine product potency, purity and consistency
- Endpoints and release specifications for drug products
- Molecular targeted therapy and patient tailored therapy - *Recent examples: GLEEVEC, HERCEPTIN. These drugs target activated and disregulated proteins, not genes.*

Regulatory Impact

- Vaccine assessment/potency
- Surrogate endpoints - efficacy/toxicity
- Quality control/quality assurance for product production
- New bioassays
- Biomarkers for early detection
- Toxicity detection and prediction

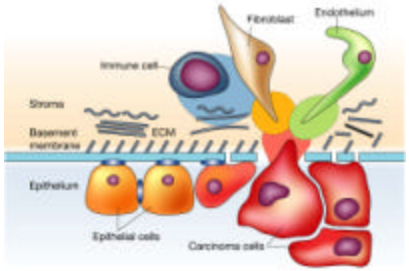
Regulatory Impact (cont.)

- Discovery of new therapeutic targets
- Risk of disease recurrence
- Patient-tailored therapy. Prospective selection
- New paradigm in disease classification/characterization
- Proteomic-based epidemiology

FDA views on proteomics:

- Critical component of safe and effective drug development
- Basis for new drug discovery, biomarkers and surrogate endpoints for toxicity and efficacy monitoring
- Means to detect and assess chemical and biological terrorist agents

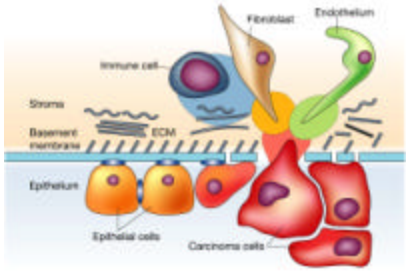
TISSUE MICROENVIRONMENT



NATURE 2001

- **Proteomic networks exist within the cell and outside the cell at the tumor-host interface**
- **Cancer is a proteomic disease at the functional level.**
- **The state of protein networks is dictated by the tissue context of the cell, and the local cell-cell or cell-matrix interactions**
- **Cell culture models may not accurately represent the fluctuating protein expression pattern and the state of protein interactions in the native tissue microenvironment**

PROTEOMIC INFORMATION



JAMA 2002

- **State of protein circuits within the cell and outside the cell at the tumor-host interface: Pathogenic role of dominant or deranged signal pathways**

- **Proteomic information content of circulating blood: Patterns of LMW proteins and peptides reflect organ pathologic states**

Keys to Cancer:

- **Early Detection-**

Development of new artificial intelligence-based bioinformatics tools for diagnostic proteomic pattern discovery

- **Molecular Diagnostics**

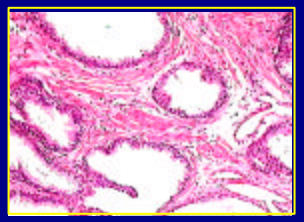
New Target Discovery (2D-PAGE)
Signal Pathway Profiling (Protein Arrays)
Phosphoproteomics (Protein Arrays/ 2D-PAGE)

- **Molecular Targeted Therapeutics**

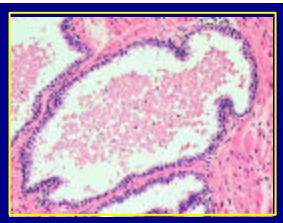
Implementation of proteomics to ongoing NCI-based clinical trials

PROTEOMIC ANALYSIS IN THE CONTEXT OF THE TISSUE MICROENVIRONMENT

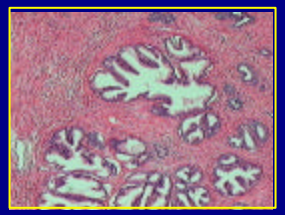
Human Prostate



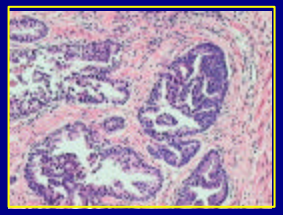
Low-grade PIN



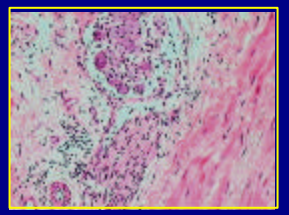
Normal



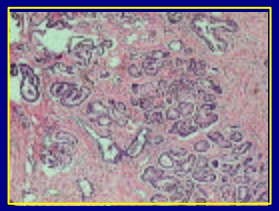
Hyperplasia



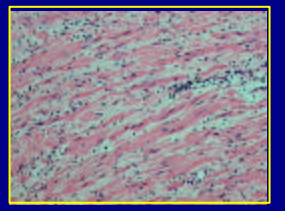
High-grade PIN



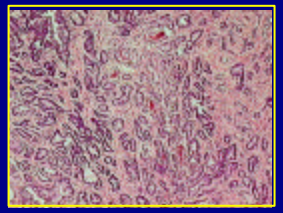
Nerve



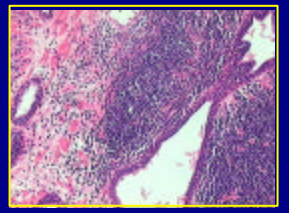
Well-differentiated carcinoma



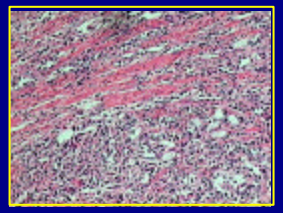
Stroma



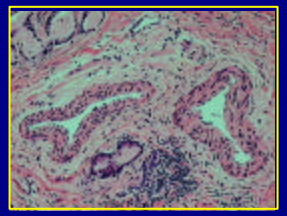
Moderately-differentiated carcinoma



Inflammation



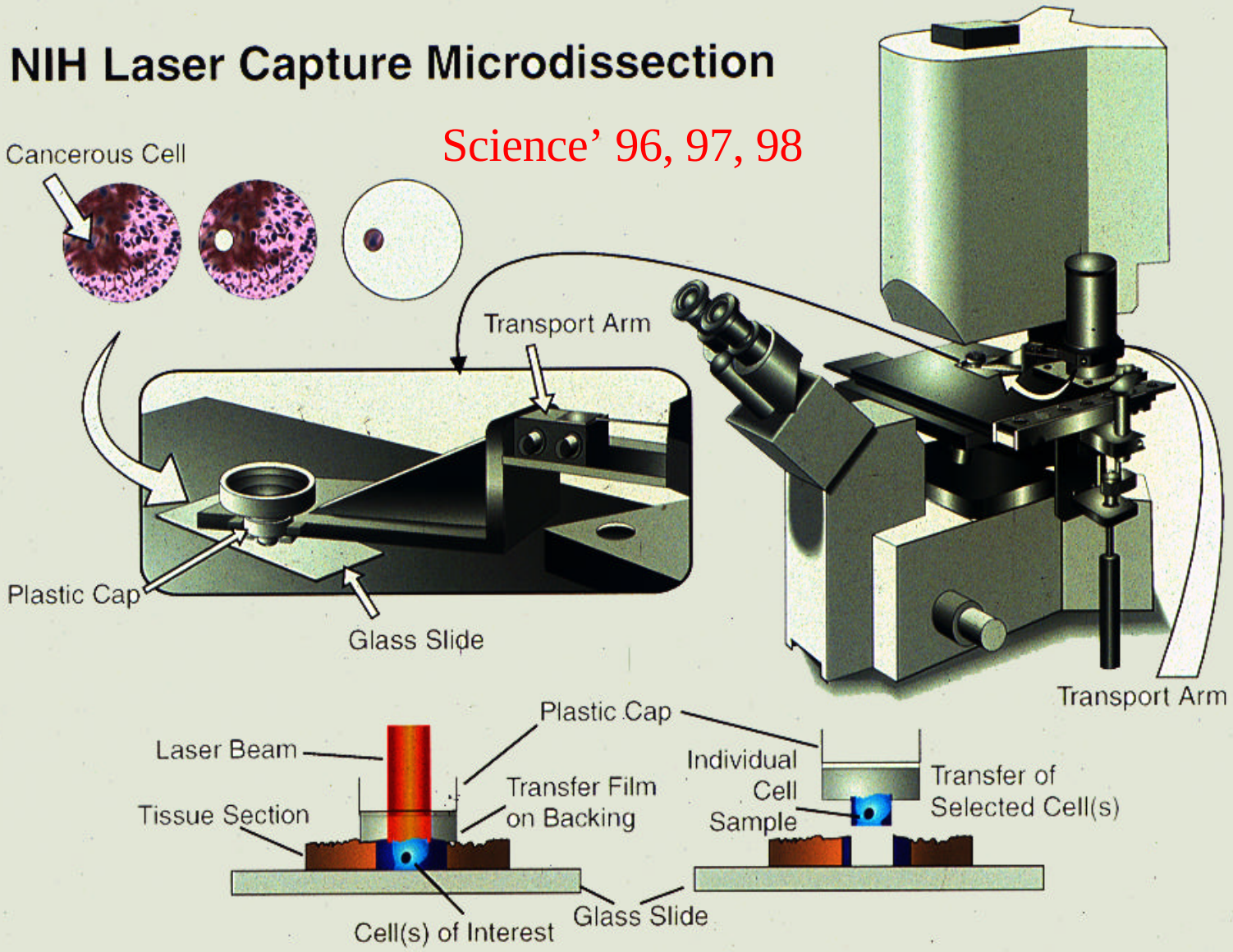
Poorly-differentiated carcinoma



Neovessels

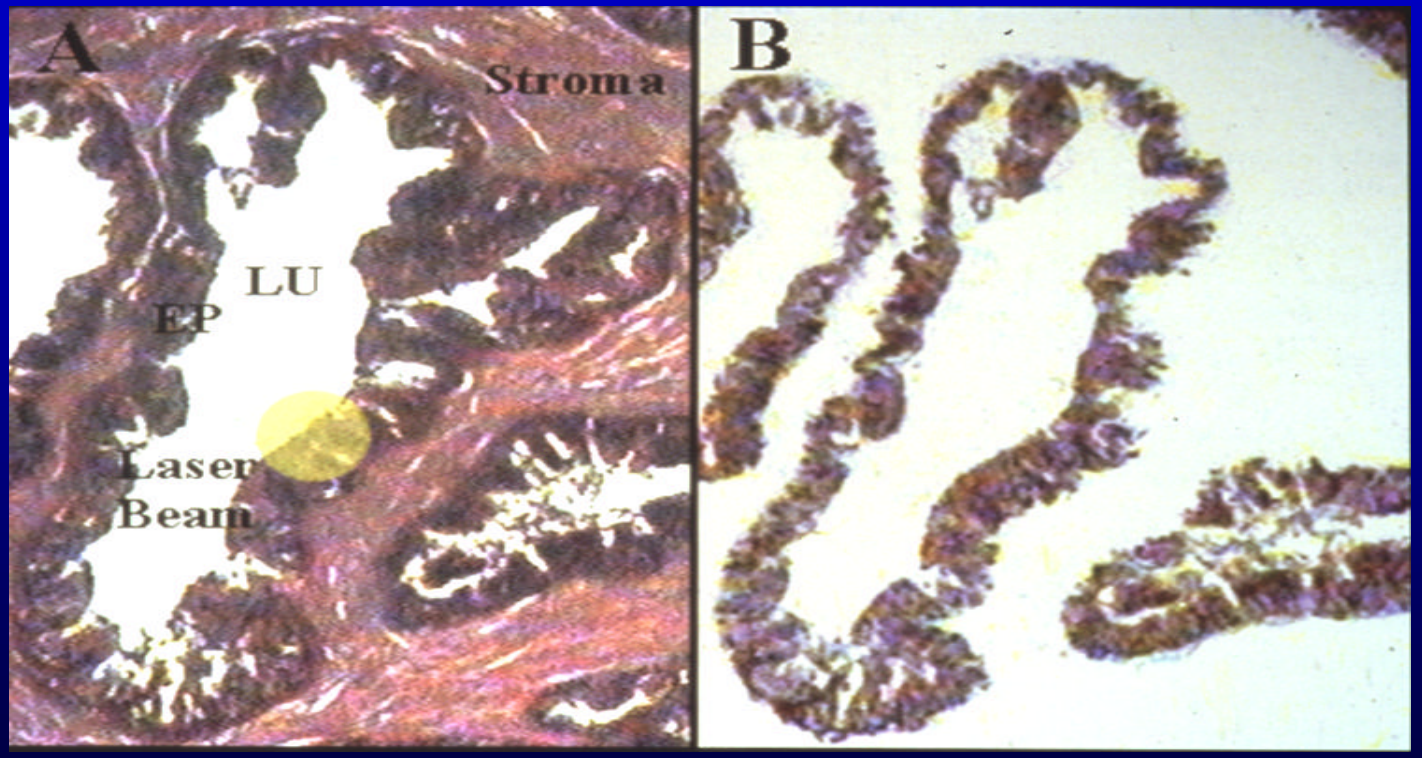
NIH Laser Capture Microdissection

Science' 96, 97, 98



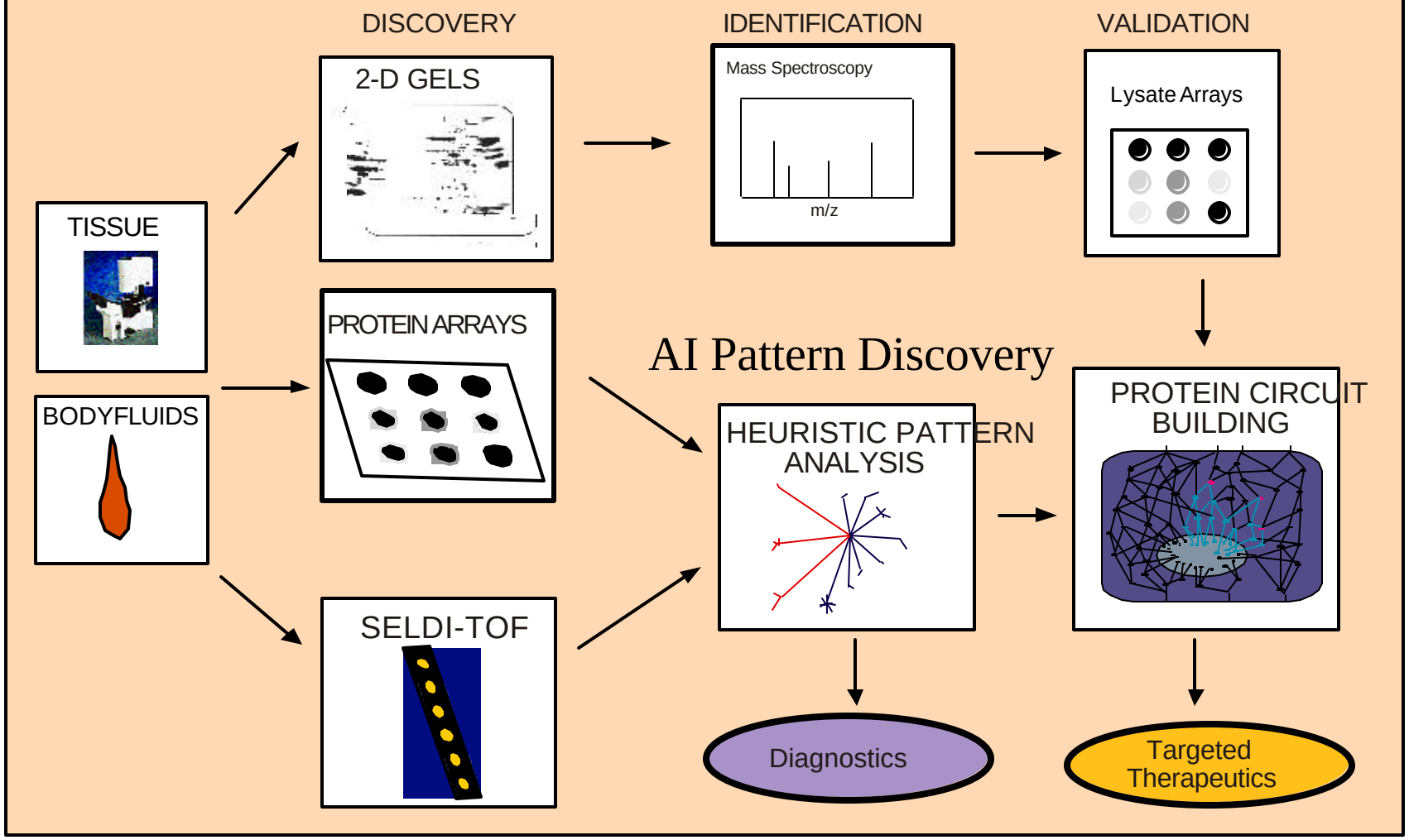
Before LCM

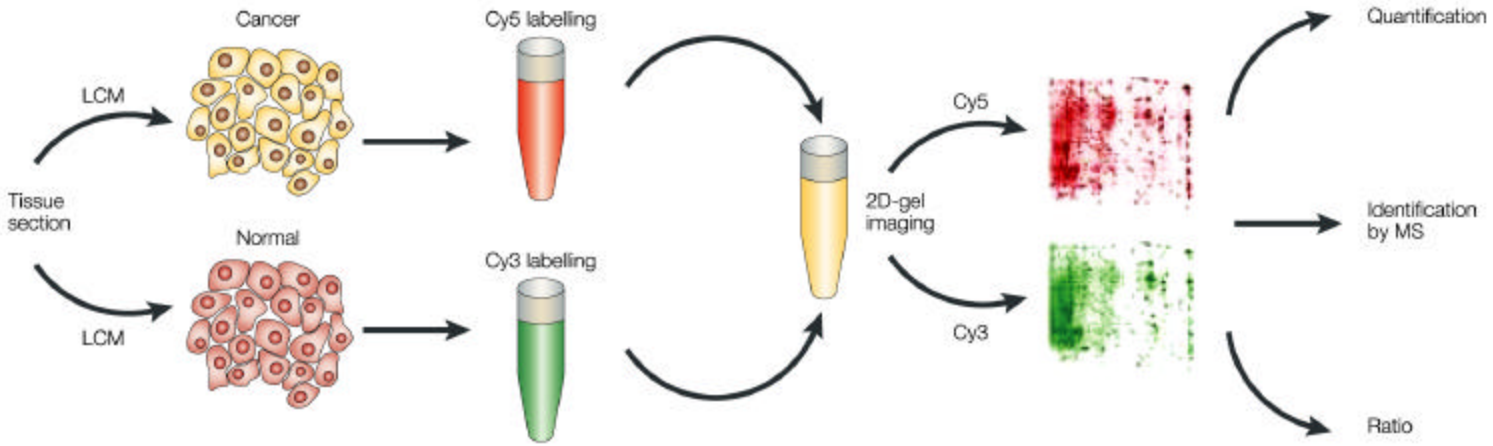
After LCM



Case study: Prostate normal epithelium (human)

NCI - CBER/FDA CLINICAL PROTEOMICS PROGRAM- Began 2000





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